Early motor repertoire and long-term neurological outcome

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CHAPTER 8

In children born preterm the quality of the motor repertoire during early infancy is associated with intelligence at school age

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Submitted

Abstract

Background: The quality of general movements (GMs) during early infancy has consistently been found to be a powerful predictor of motor disorders in later childhood. The question arises whether the quality of GMs is also associated with later cognition.

Aim: To determine whether quality of GMs in preterm children has predictive value for cognitive development at school age.

Study design: Prospective cohort study.

Subjects: The study group consisted of 60 preterm infants (36 boys, 24 girls) without cerebral palsy. The median gestational age was 30.0 weeks (range 25-33 weeks), median birth weight was 1130 grams (595-1800g). The educational level of both parents ranged from elementary to tertiary level (mothers: median 10 years, range 6-17 years, fathers: median 11 years, range 8-17 years). The quality of GMs was prospectively assessed as normal or abnormal from video- recordings that were made at regular intervals: at preterm age, term, three to eight weeks' post-term, and at eleven to seventeen weeks' post-term age.

Outcome measures: At seven to eleven years of age, the children's intelligence was tested using the WISC-III^{NL}. The total (TIQ), verbal (VIQ) and performance (PIQ) intelligence quotient scores were calculated.

Results: The median TIQ was 93 (67-113), VIQ 96 (68-117), and PIQ 92 (65-119). Fifteen children (25%) had a low TIQ (<85). The longitudinal course of the quality of GMs was associated with TIQ, VIQ, and PIQ. If the quality of GMs had normalised before eight weeks' post-term, TIQ, VIQ, and PIQ fell within the normal range. A consistently abnormal quality of GMs before eight weeks' post-term was associated with a lower TIQ, VIQ, and PIQ. The likelihood ratio of consistently abnormal GMs up to eight weeks post-term for a low TIQ was 4.9 (95%CI: 1.4-17.2). The educational levels of the parents were not associated with IQ scores.

Conclusions: The quality of GMs during the early post-term period is a predictor for intelligence at school age. Abnormal quality of GMs during the early post-term period may reflect injury or developmental disruptions of brain areas involved in cognitive development. It may also reflect the crucial role of motor activity in normal cognitive development.

Introduction

Children born preterm have significantly lower IQ scores than their term peers, even in the absence of brain lesions or severe disability, or both.[1] It is estimated that cognitive and behavioural deficits occur in 25 to 50% of children born preterm with very low birth weight (birth weight below 1500g).[1-3] Cognitive problems without major motor deficits are by far the most dominant neurodevelopmental sequelae in children born preterm. Studies reported that the intelligence quotient (IQ) is approximately four to ten points lower in children born before 32 weeks' gestational age in comparison to their term peers.[1,3] It is estimated that by each week of shorter gestation below 32 weeks, the IQ is approximately 1.7 points lower.[2] This increases to 2.5 points by each week below 27 weeks' gestational age.[1] These impairments become more evident at school age, when the child faces more complex cognitive demands.

In early infancy, it is difficult to identify the individual infant at highest risk for poor cognition. Models of pathogenesis include changes related to developmental disruptions and brain injury.[3,4] Although global white matter damage revealed by magnetic resonance imaging is quite common in children born preterm, and volumes of gray matter are also diminished, clear associations of cognition with

pathological changes on neuro-imaging have not been demonstrated beyond doubt.[5-7]
Prechtl's method of the qualitative assessment of general movements (GMs) in infants is a reliable, sensitive, and non-intrusive method to assess the integrity of the brain at an early age. The assessment of GMs is based on Gestalt perception. It takes into account the complexity and variability of the movement. Normal GMs are complex, variable, and elegant, reflecting variability of neural function. Abnormal GMs lack complexity, variability, and fluency. The quality of GMs during early infancy has, consistently, been found to be a powerful predictor of motor disorder in later childhood.[8-13] Nevertheless, the predictive value of the quality of GMs for later cognition is still unclear. The objective of this study was, therefore, to investigate whether the quality of the early motor repertoire up to the age of seventeen weeks' post-term had predictive value for intelligence and school performance at seven to eleven years of age.

Methods

Subjects
The study group consisted of children born preterm between September 1992 and October 1997 and who had been admitted to the Neonatal Intensive Care Unit (NICU) of the Beatrix Children's Hospital of the University Medical Center Groningen (UMCG), the Netherlands. They were included in prospective cohort studies on the prognostic value of the quality of GMs for major motor impairments at school age[9,14-16] and minor neurological dysfunctions.[13,17] All infants were born before 34 weeks' gestational age and written parental consent was obtained during the first week after birth. The UMCG's ethical review board approved the study.
For the present study we excluded the infants who had developed cerebral palsy by the age of at least six years, based on Bax' criteria.[18] The final study group consisted of 60 children (36 boys and 24 girls), whose median gestational age was 30.0 weeks (range 25-33 weeks) and a median birth weight of 1130 grams (range 595-1800g). The educational level of the parents ranged from elementary to tertiary level (mothers: median 10 years, range 6-17 years, fathers: median 11 years, range 8-17 years).
The children included in the study can be considered typical of the preterm infants admitted to the tertiary NICU of the UMCG in the mid 1990s, who did not develop severe neurological disorders. The children's medical characteristics and the educational levels of the parents are presented in Table 1.

Recording and evaluation of the motor repertoire
Video-recordings of approximately 60 minutes were made of the infants from the first or second week after birth and subsequently at weekly intervals until discharge. Additional recordings of approximately ten minutes were made of the infants at term age (38 – 42 weeks' postmenstrual age), between three and eight weeks' post-term age, and between eleven and seventeen weeks' post-term age. These recordings were made either at the outpatient clinic or at home, during periods of

Table 1. The clinical characteristics and risk factors of the study group according to the cognitive findings at school age. Data are expressed as median (P25-75), or N (%).

	Children who had a total IQ ≥ 85	**Children who had a total IQ < 85**
Number	45	15
Age of IQ assessment	9.2 years (8.6-9.3 years)	8.6 years (9.2-10.1 years)
Maternal educational level	10 years (9-12 years)	11 years (9-12 years)
Paternal educational level	11 years (10-14 years)	11 years (9.8-13.3 years)
Gestational Age	30.0 weeks (28.6-31.1 weeks)	30.0 wk (27.4-31.7 weeks)
Birth Weight (BW)	1120 g (905-1288 g)	1215 g (980-1460 g)
Male gender*	24 (53)	12 (80)*
IUGR (BW < P5)[1]	14 (31)	2 (13)
Prenatal corticosteroids	28 (62)	11 (73)
Apgar score at 5'	8 (7 – 9)	8 (5 – 9)
Umbilical pH	7.26 (7.21-7.31)	7.28 (7.24-7.32)
Ventilatory support (IPPV of HFOV)[2]	25 (56)	7 (47)
Septicaemia	19 (42)	3 (20)
ICH[3] gr1-2	12 (27)	3 (20)
PVL[4] gr1	20 (44)	8 (53)
BPD[5]	12 (27)	4 (27)
Postnatal corticosteroids	6 (13)	1 (7)

[1] IUGR is intra-uterine growth restriction, birth weight according to the Dutch weight centiles of Kloosterman.[19]

[2] IPPV is intermittent positive pressure ventilation, HFOV is high frequency oscillatory ventilation.

[3] ICH is intracranial haemorrhage graded according to Papile *et al* .[20]

[4] PVL is periventricular leukomalacia graded according to De Vries *et al* .[21] PVL grade 1 is also called prolonged flaring.

[5] BPD is Bronchopulmonary dysplasia, defined as oxygen dependency at 36 weeks' postmenstrual age.

* p=0.078

active wakefulness between feeds, with the partly dressed infants lying in supine position.
For each infant a median of ten recordings (interquartile range [IQR] 8-11) were available for analysis. The recordings were ordered according to age to obtain a developmental trajectory of the individual child. All recordings were evaluated off-line by JLMB and AFB, according to Einspieler *et al*.[22,23] One of the observers was unaware of the infants' clinical history and developmental status; one knew the infants' clinical history but was unaware of their developmental status at school age.

The assessment of the quality of GMs up to the age of eight weeks post-term

From the video-recordings made during the period up to eight weeks' post-term, the quality of the GMs was assessed as normal or abnormal, according to Einspieler *et al*.[22,23] Normal GMs are characterised by complexity, variability, and fluency, whereas abnormal GMs display reduced

complexity, variability, and fluency. In case of abnormal GMs, three categories of abnormal GMs were distinguished: 1) *poor repertoire* GMs, 2) *chaotic* GMs and 3) *cramped synchronised* GMs.[22,23] Previous studies reported interobserver reliabilities with kappas between 0.8 and 0.9.[22,24,25]

For further analysis we clustered the results based on the individual developmental trajectories of quality of GMs up to eight weeks' post-term age into five categories: 1. Consistently normal. 2. Abnormal, normalising during preterm period (before 38 weeks' postmenstrual age). 3. Abnormal, normalising during term period (38 to 42 weeks' postmenstrual age). 4. Abnormal, normalising during early post-term period (between three and eight weeks' post-term). 5. Consistently abnormal GMs up to eight weeks' post-term.

The assessment of the quality of the motor repertoire between eleven and seventeen weeks of post-term age

From the recordings made between eleven and seventeen weeks' post-term, we assessed the quality of fidgety general movements, also called fidgety movements (FMs). Normal FMs are continuous small movements of moderate speed in all directions. FMs are present obligatory between nine and sixteen weeks' post-term, but in many cases they were present as early as six weeks and as late as twenty weeks' post-term age. Apart from FMs, the quality of the concurrent motor repertoire was assessed, according to Bruggink *et al*.[13,17]

The quality of FMs was classified as normal or abnormal. We distinguished between two types of abnormal FMs: 1. Abnormal FMs (FMs with exaggerated speed, amplitude, and jerkiness). 2. Absent FMs (no FMs observed).[25] The quality of the concurrent motor repertoire was assessed as normal or abnormal based on the performance of all movement and postural patterns. A normal concurrent repertoire was scored if it was smooth, fluent, and variable, an abnormal motor repertoire was scored if it was monotonous, jerky, tremulous, or cramped.[13] A previous study showed a high interobserver variability with a kappa of 0.91.[13]

For further analysis, the results of individual qualitative assessments of FMs and the concurrent motor repertoire were combined and clustered into three categories: 1. Normal FMs, normal concurrent motor repertoire. 2. Normal FMs, abnormal concurrent motor repertoire. 3. Abnormal FMs or absence of FMs, abnormal concurrent motor repertoire.

The assessment of cognitive function at the age of seven to eleven years

The Wechsler Intelligence Scale for Children III, Dutch Version (WISC III^{NL})[26] was performed between seven and eleven years of age. We used four Verbal subscales (Similarities, Vocabulary, Information, Arithmetic) and three Performance subscales (Picture Arrangement, Block Design, Object Assembly). Verbal (VIQ), Performance (PIQ), and Total (TIQ) intelligence quotient scores were calculated using Sattler's formula.[27] With regards to school performance we documented whether the children had repeated one or more classes, or whether they attended special education.

Statistical analysis

Statistical analysis was performed using SPSS package for Windows, version 16.0. In contrast to the scores of the quality of GMs, the intelligence scores were normally distributed. Non-parametric tests were used to relate IQ scores with the quality of GMs. These included the Mann-Whitney U test, Spearman's Rank test, and the Kruskal Wallis test. For categorical variables, the Chi-square test for trend or Fisher's exact test was used. Sensitivity, specificity, positive, and negative predictive values of the quality of GMs as a marker for later abnormal IQ scores (<85) were calculated. Backwards stepwise logistic regression was used to determine if assessment of GMs could predict intelligence at school age after controlling for clinical and social factors. These factors included the educational level of both parents and factors that were significant at $p<0.1$ in the univariate analyses. A two-tailed probability value of $p<0.05$ was considered to be statistically significant.

Results

The developmental trajectories of the quality of GMs

The number of children with normal or abnormal GMs during each period is displayed in Table 2. Eighteen children (30%) had consistently normal GMs from birth onwards; in another four children (7%) GMs normalised before term age. Fifteen children (25%) had abnormal GMs of a poor repertoire during preterm period, but normalised GMs at term (n=14) or during the early post-term period (n=1). Twenty-three children (38%) had consistently abnormal GMs up to eight weeks' post-term. In the majority of cases these GMs had a poor repertoire; two children had cramped synchronised

Table 2. The number of children with a normal and abnormal quality of GMs until seventeen weeks' post-term, during five periods: early preterm late preterm, term, early post-term, and late post-term period. FMs are the GMs during the late post-term period. The numbers in the boxes represent the numbers of children. With increasing age the proportion of infants with normal GMs increased significantly (Chi^2 for-trend-test $p<0.001$)

	Early preterm (<34 weeks)	Late preterm period (34-37 weeks)	Term period (38-42 weeks)	Early post-term period (3-8 weeks)	Late post-term period (11-17 weeks)
Normal GMs	18	22	36	37	
Normal FMs, N repertoire					30
Normal FMs, A repertoire					16
Abnormal GMs	42	38	24	23	
Abnormal FMs or absence of FMs					11

GMs: general movements, FMs: fidgety movements, N: normal, A: abnormal.

GMs on one occasion.

As there was only one child in whom GMs normalised during the early post-term period, this child was analysed in the category of children who normalised at term. For further statistical analyses this combined group was regarded as a single group.

Between eleven and seventeen weeks, the quality of FMs and concurrent motor repertoire could not be assessed in three children due to crying, sleepiness, or hiccups. Of the remaining 57 children, 30 (53%) had normal FMs and a normal quality of the concurrent motor repertoire, sixteen (28%) had normal FMs with an abnormal concurrent repertoire, ten (18%) had abnormal FMs, and in one child (2%) FMs were absent. With increasing age, the proportion of children with abnormal GMs or FMs decreased significantly (Table 2, chi^2 for-trend-test, $p<0.001$).

The cognitive findings at school age

The median age of children during testing was 9.0 years (range 7.1 – 11.2 years). The median TIQ was 93 (67-113), VIQ 96 (68-117), and PIQ 92 (65-119). Fifteen children (25%) had a low TIQ (<85). Five children (8%) attended schools for special education. Another sixteen children (27%) had repeated a class in primary school. Thirty-nine children (65%) attended primary school without repeating a class up to the moment of testing.

The relation between the quality of GMs and findings at school age

The TIQ scores of the children categorised according to the individual developmental trajectories of the quality of GMs up to eight weeks' post-term age, are graphically displayed in Figure 1. If the

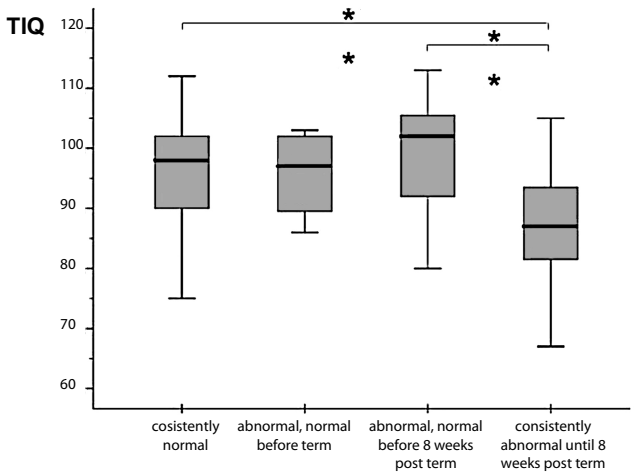

Figure 1. The relation between the quality of GMs up to eight weeks' post-term age and TIQ scores at school age. The differences between the groups were tested by Mann Whitney U tests. (* = $p<0.05$; ** = $p<0.01$; *** = $p<0.001$).

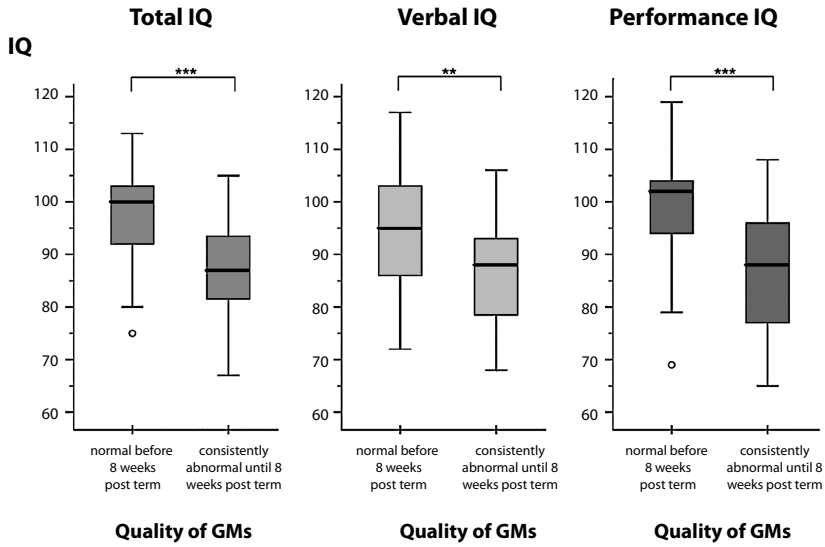

Figure 2. The relation between the quality of GMs up to eight weeks' post-term age and TIQ, VIQ, and PIQ. The differences between the groups were tested by Mann Whitney U tests. (* = p<0.05; ** = p<0.01; *** = p<0.001).

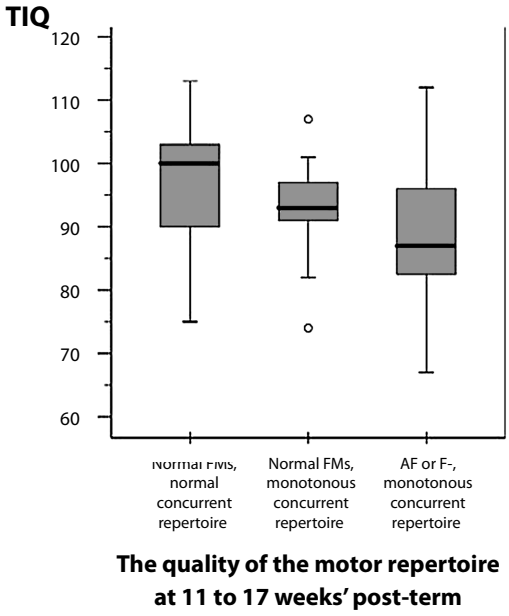

Figure 3. The relation between the quality of the motor repertoire at eleven to seventeen weeks' post-term and TIQ scores at school age.

quality of GMs normalised before eight weeks' post-term age, the median TIQ was 100 (range 75-113), VIQ 95 (72-117), and PIQ 102 (69-119). There was no difference in TIQ, VIQ, and PIQ between children who showed normal GMs consistently and children who showed abnormal GMs initially, but normalised before eight weeks' post-term age (Figures 1 and 2). In children showing abnormal GMs consistently up to eight weeks' post-term age, IQ scores were significantly lower: the median TIQ

Table 3. The relation between the quality of GMs up to eight weeks' post-term and IQ scores at school age. The numbers in the boxes represent the numbers of children. Sensitivity, specificity, PPV, and NPV rates are stated below the table.

	IQ < 85	IQ ≥ 85	Total
Consistently abnormal GMs until eight weeks' post-term	10	13	23
Normal GMs before eight weeks' post-term	5	32	37
Total	15	45	60

Sensitivity:	67% (95% CI: 43-91%)
Specificity:	71% (95% CI: 58-84%)
PPV:	43% (95% CI: 23-63%)
NPV:	86% (95% CI: 75-97%)

GMs: general movements, IQ: intelligence quotient, PPV: positive predictive value, NPV: negative predictive value; CI: confidence interval.

was 87 (67-105) (Mann Whitney U, $p<0.001$), VIQ 88 (68-106) ($p<0.01$), and PIQ 88 (65-108) ($p<0.001$, Figures 1 and 2). There was no association between the quality of the early motor repertoire at eleven to seventeen weeks' post-term age (FMs and the concurrent motor repertoire) and TIQ scores (Kruskal Wallis test $p=0.129$) (Figure 3).

School performance was also associated with the quality of GMs up to eight weeks' post-term. Nine out of 37 children (24%) in whom GMs normalised, had repeated a class or had attended special education, versus twelve out of 21 children (57%) in whom GMs did not normalise before eight weeks' post-term age (Fisher's exact, $p=0.050$).

If a TIQ score of 85 was taken as the cut-off point for abnormal cognition, the quality of GMs between term age and eight weeks' post-term age predicted cognitive functioning at school age (Table 3). The sensitivity was 67% (95% CI: 43-91%), specificity 71% (95% CI: 58-84%), positive predictive value 43% (95% CI: 23-63%), and negative predictive value 86% (95% CI: 75-97%). No other clinical and social factors were significantly associated with a low TIQ. There was a trend, however, for male gender and low TIQ scores ($p=0.078$) (Table 1).

The likelihood ratio of consistently abnormal GMs up to eight weeks' post-term for a low TIQ was 4.9 (95%CI: 1.4-17.2, $p=0.013$). This explained 15.6% of the variance of the TIQ scores. After entering male gender and the educational level of the parents in the model, only the quality of GMs remained in the model. In this model, the likelihood ratio of consistent abnormal GMs up to the age of eight weeks post-term for a low TIQ was 4.9 (95%CI: 1.3-17.6, $p=0.016$). This explained 22.4% of the variance of TIQ. Regarding school performance (special education and repeating a class), the likelihood ratio of consistent abnormal GMs was 3.4 (95%CI: 1.1-10.3, p=0.031) explaining 10.6% of the variance of school performance.

Discussion

This study demonstrates that in children born preterm, intelligence at school age is associated with the quality of their GMs during early infancy. The quality of GMs during the early post-term period, in particular, proved to be a predictor for intelligence at school age. If GMs normalised before or at term age, IQ scores were within normal limits. If, however, GMs were consistently abnormal up to eight weeks' post-term age, IQ scores at school age were on average 13 points lower, i.e. 0.9 standard deviation. Normalisation of GMs before term age did not differentiate between normal and lower IQ scores. Moreover, the quality of FMs and the concurrent motor repertoire at eleven to seventeen weeks' post-term age did not differentiate between normal and lower IQ scores.

We found that the IQ scores of children is this study were within the same range as in other studies performed in preterm, non-disabled children.[1,3,28] The proportion of children who attended special education or had repeated classes, were also similar to previous reports.[29,30] Executive functions, as measured by the PIQ, were worse than complex language functions, measured by the VIQ. This finding was in line with previous studies.[1,6,30,31] It is interesting to note that not only PIQ, but also VIQ was strongly related to the quality of GMs during the early post-term period. The abnormal quality of GMs during the early post-term period may reflect injury or developmental disruptions of brain areas involved in cognitive development.[3,4] Recently, a clear association was observed between abnormal GMs at the age of one and three months post-term, and abnormalities of the cerebral white matter on magnetic resonance imaging at term-equivalent age.[32] This association was not seen between abnormal GMs and gray matter abnormalities.[32]

Diffuse damage of the white matter is the most commonly observed abnormality of the brain of preterm infants.[7,32,33] White matter damage results in hypomyelination, neuronal disease and widespread axonal degeneration in the cerebral cortex, thalamus, basal ganglia, and cerebellum that can be seen as early as term-equivalent age.[4,34] Several studies showed that in preterm infants cerebral white matter damage, in particular, is related to cognitive dysfunction at school age, usually in the absence of major motor deficits.[6,33,35] In most studies, the relation of cognitive function with cerebral white matter pathology is at least as strong[7], or even stronger, than cerebral gray matter pathology.[3,32,33]

Our results support the notion that reduced complexity and variability of GMs – as an expression of cerebral white matter damage[14] – is the motor correlate of impaired cognitive functioning, in particular of those cognitive functions relying on widely distributed cortical networks.[36] It may reflect the vulnerability of the critical time frame during which the human cerebrum develops rapidly. Normally, cerebral cortex volume increases about four times during the third trimester of pregnancy and the first postnatal weeks.[4] Diffuse cortical white and gray matter damage may result in volumetric deficits in multiple cortical regions.[37] This has also been related to a wide variety of cognitive deficits observed at follow-up.[7,37] Abnormal GMs at term and during the early post-term period may be a predictor for the heightened vulnerability of the rapidly developing brain during

this particular period of maturation.

We suggest that our results may also reflect the crucial role of motor activity in normal cognitive development. A possible interpretation could be that motor activity during the early post-term period (as reflected by GMs) plays an important role in the early development of cognition.[38] Some aspects of the motor repertoire at three to four months' post-term are associated with cognitive outcome at school age.[39] Rapid brain development in the early post-term months is accompanied by equally rapid psychological development.[40] The infants' exploration of their environment with several motor strategies, integrating and refining neural input and output, may lead to better neurological development.[41] The absence of a complex and variable motor repertoire at this particular age might hamper the infants' abilities to interact with the world around them. This implies that the quality of the early motor repertoire is a measure of the extent to which spontaneous movements facilitate or inhibit infants' interactions during a phase in which sensorimotor activity drives perceptual and cognitive development.[42]

Although some studies showed a significant association between motor development and cognitive abilities at a later age, e.g. four years,[43,44] the present study is among the few that investigated the association between motor development at such a young age and cognition at school age.

Clinical and social factors did not contribute to the prediction of intelligence at school age. Only male gender showed a trend towards lower IQ scores. Previous studies also showed a similar association between intelligence and gender.[1,30] Other studies reported that socio-economic status of the parents and gestational age are associated with intelligence in preterm infants.[1,2] Due possibly to the relatively small sample size, our study did not confirm these findings. Nevertheless, even large studies have failed to identify specific risk factors, other than prematurity, for the development of cognitive deficits in the absence of major motor disabilities.[2,45,46] The assessment of the quality of GMs at term and the early post-term period may, therefore, be helpful in determining the individual risk of preterm infants to develop clinically relevant cognitive impairment at school age.

We recognise a few limitations to the present study. First, we did not include a term control group. Since we do not know, for example, how often an abnormal quality of GMs is present in term infants, these results cannot be generalised and have still to be confirmed in other groups of children. A second limitation is that there might have been a selection bias because the infants had taken part in several earlier studies. Nevertheless, we consider the children in the present study to be a representative sample of a third level neonatal intensive care unit. We included both low and high risk preterm infants. A final limitation is the study sample size. The results are based on data from a small group of children from one medical centre only. The below average mean IQ scores of the participants were similar to those found in other follow-up studies of children born preterm.[1,2] While this increases our confidence that these results can be generalised to the broader population of children born preterm, further investigations are warranted.

Conclusion

The quality of GMs during the early post-term period predicts intelligence at school age. The integrity of those areas of the brain involved in abnormal GMs during the early post-term period may be important for cognitive development at school age. It may also reflect the crucial role of motor activity in normal cognitive development. Our findings enable non-invasive and early identification of individual preterm infants at increased risk for cognitive impairment. They also enable the early identification of individual preterm infants at low risk for development cognitive impairments.

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